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Long-term oxygen therapy improves health-related quality of life ☆

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Summary Guidelines for the prescription of long-term oxygen therapy (LTOT) in hypoxemic COPD patients are based on two landmark studies in which survival was the primary outcome. Such patients are importantly symptomatic with poor health-related quality of life (HRQL) but the effect of LTOT on HRQL remains uncertain.

We undertook a prospective longitudinal interventional study of consecutive COPD patients referred to our regional oxygen service; $n = 43$ fulfilling criteria and commenced on LTOT, $n = 25$ not fulfilling criteria and continued on standard care. HRQL was measured at baseline, 2 and 6 months.

Both patient groups had severe COPD as defined by mean $FEV_1 < 35\%$ predicted. At baseline the LTOT group demonstrated significantly worse HRQL as defined by the Chronic Respiratory Questionnaire (CRQ) (fatigue, emotional function, mastery and total scores), total generic Dartmouth COOP Charts and anxiety domain of the Hospital Anxiety and Depression scale. Significant improvements in HRQL were noted at 2 and 6 months in the LTOT group. Conversely the non-LTOT group demonstrated a progressive decline in HRQL. Using validated criteria for a minimal clinically significant improvement in CRQ, there were 28 (67%) and 26 (68%) 'responders' at 2 and 6 months respectively in the LTOT group.

The introduction of LTOT to patients with severe COPD fulfilling standard criteria was associated with early significant improvements in HRQL with sustained or further response at 6 months.

Introduction

Current guidelines for the prescription for long-term oxygen therapy (LTOT) for patients with chronic hypoxia and chronic obstructive pulmonary disease (COPD) rely on two landmark studies performed over 20 years ago in which survival was the primary outcome.[1–3] In the Nocturnal Oxygen Therapy Trial (NOTT) study mortality was as low as 11.9% and 22.4% at 1 and 2 years respectively in the continuous oxygen arm.[1] However, in clinical practice these survival advantages may not necessarily be achieved. McCallion et al.[4] reported a 50% mortality rate within the first 3 months of LTOT. Other studies cite 54% mortality at 2 years[5] and 60% mortality at 3 years.[6] Our local experience has also noted a disturbingly high 6 month mortality rate of 33%.[7] These high mortality rates are sobering, and likely reflect the clinical reality of LTOT prescription generally. Thus although the merits of LTOT are well accepted in regard to survival and the validity of prescribing LTOT in patients with severe COPD who satisfy rigorous criteria is not in question, these results do challenge the premise that the only role of LTOT is to improve survival. The

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negative impact of COPD on health-related quality of life (HRQL) is substantial[8–10] and the use of HRQL as an appropriate primary outcome measure is no longer in dispute. Generally, therapy in COPD remains largely symptomatic and aimed at enhancing life (adding quality to years). These LTOT patients with severe symptomatic COPD are significantly disabled and may rate improvement in HRQL more highly than any possible, and perhaps quite small, survival advantage.

Unfortunately HRQL was not a primary outcome measure in the original landmark studies, albeit meagre improvements in neuropsychological function were reported in the NOTT trial.[1,11] There was no improvement in HRQL as captured by the Sickness Impact Profile, although Jones et al.[12] have shown that this instrument is insensitive, and the lack of a disease-specific tool may have accounted for the negative result. In the Medical Research Council trial HRQL was not specifically assessed.[2] Any subsequent studies were disadvantaged in that a randomised placebo-controlled design would have been deemed unethical. The few longitudinal studies have been non-randomised and further hampered by deficiencies such as patient numbers, potential confounders or limitations with HRQL tools. A small study by Lahdensuo et al.[13] attempted only to examine the psychosocial response to LTOT and reported no significant changes. Subsequently, Okubadejo et al.[14] using a disease-specific HRQL tool were unable to show a change in HRQL over a 6 month period. However, a larger study has reported some clinically significant improvements in HRQL in females, although the response in males was less convincing.[15] There is evidence that the mode of oxygen delivery may be influential. A study by Andersson et al.[16] demonstrated that, for patients ambulant outside the home, HRQL improved with liquid oxygen but deteriorated with oxygen provided by a concentrator and cylinders for ambulation. However liquid oxygen is more expensive and concentrators remain widely used for the provision of LTOT. Furthermore, a considerable proportion of LTOT patients are known to be housebound and hence not suitable candidates for an ambulatory supply.[17,18] Accordingly considerable uncertainty remains as to whether LTOT as provided by an oxygen concentrator improves HRQL. Conversely, it is important to ascertain that LTOT does not adversely affect HRQL.

This prospective longitudinal interventional study aimed: (1) to determine the changes in HRQL following introduction of LTOT in COPD patients who fulfil standard criteria, (2) to examine whether baseline characteristics are predictive of clinically significant improvements in HRQL and (3) to compare these changes in HRQL in patients on LTOT with that of a group of severe COPD patients referred over the same period for LTOT but who did not fulfil criteria for LTOT.

Methods

Figure 1 outlines the study design. Consecutive patients with COPD referred to our Regional Oxygen Service for LTOT assessment were invited to participate. Local Ethics Committee approval was obtained with signed consent from all participants.

Inclusion criteria:

(i) severe COPD (British Thoracic Society),[3]
(ii) standard medical management,
(iii) clinically stable at least 2 months.

Exclusion criteria:

(i) substantive comorbidity,
(ii) current smoker,
(iii) inability to complete questionnaires.

Patients were assessed for LTOT using standard criteria[3]

(a) $PaO_2 < 7.3$ kPa (55 mmHg) at rest or
(b) PaO_2 7.3−8 kPa (60 mmHg) plus significant pedal oedema, *P* wave >3 mm standard electrocardiograph leads or secondary polycythemia (packed cell volume >0.55).

LTOT group

Defined as fulfilling criteria for LTOT and supplied with oxygen.

Non-LTOT group

Defined as not fulfilling for LTOT and not supplied with oxygen.

The LTOT group received standardised instruction regarding their oxygen therapy (Invacare 5 concentrators, Invacare Corp, Elyria, Ohio USA). Flow was titrated to achieve resting $PaO_2 > 8$ kPa ($SaO_2 > 90\%$). Adherence was defined as mean use of at least 15 h daily (hour-meter). Ambulatory oxygen was not provided.

Data collection

Arterial blood gases were measured at rest breathing room air for at least 20 min. Spirometry was

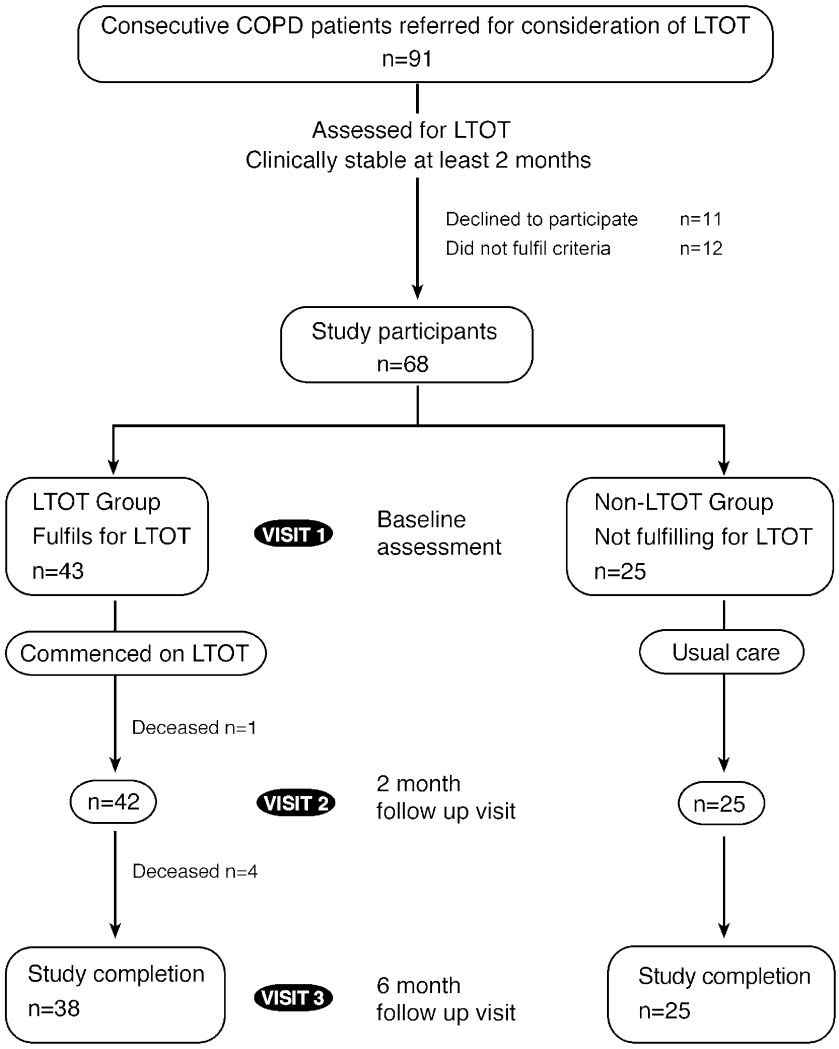

Figure 1 Study design and patient group details.

performed to ATS standards (R-Model Vitalograph Limited, Buckingham, England). The 6 min walk test (6MWT) was performed in triplicate on room air with measures of distance, oxygen saturation (SpO_2) and modified Borg dyspnoea scores.[19] Questionnaires were administered at each visit, using the preceding 2 weeks as the indicative period.

Chronic respiratory questionnaire (CRQ)[20–22]

This validated, repeatable and responsive disease-specific interviewer-administered instrument has four domains; dyspnoea, fatigue, emotional function, and mastery. Each answer is scored from 1 to 7 (7 = optimal). Responders were defined using validated criteria for a minimal clinically significant difference; an improvement of 0.5 in the mean score of each domain[21] equating to a dyspnoea change of at least 2.5, fatigue 2, emotional function 3.5 and mastery 2, respectively.

Dartmouth COOP charts (COOP)[23]

This self-administered generic HRQL instrument has 9 charts; physical function, daily activities, pain, social activities, social support, feelings, overall health, quality of life and change in health. Responses are scored by a 5-point ordinal scale ranging from 1 to 5 (1 = optimal).

Hospital anxiety and depression scale (HAD)[24]

This is a reliable self-assessment scale used for evaluating anxiety and depression in the physically ill, scores ranging from 0 to 21 (0 = optimal).

Patient expectations

Patient expectations were explored using the following question; "Do you think that oxygen will

(has) improved your quality of life?'' (1 = strongly disagree, 2 = tend to disagree, 3 tend to agree, 4 = strongly agree).

Statistical analyses

Results are presented as means (standard deviations) or means (95% confidence intervals). Continuous variables between groups were compared with Student's *t*-test and the χ^2 or Fisher's exact test for categorical variables. Normality was checked both graphically and with Shapiro–Wilk statistics. Associations between responder status and other risk factors were examined using logistic regression (with responder/non-responder to oxygen as the outcome measure).

Results

A total of 68 patients were recruited; 43 fulfilling criteria and supplied with LTOT (LTOT group) and 25 not fulfilling LTOT criteria and not supplied with oxygen (non-LTOT group). Baseline group characteristics were as shown in Table 1. All had severe COPD, as defined by FEV_1 criteria but those fulfilling LTOT criteria had significantly worse gas exchange and functional capacity (6MWD). There were 5 deaths over the 6 months study period in the LTOT group and none in the non-LTOT group.

Baseline HRQL

The LTOT group demonstrated significantly worse HRQL at baseline than the non-LTOT group as defined by the disease-specific CRQ (total and all domains except dyspnoea), generic COOP total and the HAD anxiety domain (Table 2).

Change in HRQL at 2 and 6 months

In the LTOT group significant improvements were seen in all domains of the CRQ by 2 months which at 6 months were either maintained or further improved (Fig. 2). Improvements demonstrated in the total COOP and both HAD domains did not reach statistical significance. Conversely, HRQL measures in the non-LTOT group, although significantly higher at baseline than the LTOT group, deteriorated over the study period such that by 6 months the HRQL of the 2 groups was not significantly different. No significant changes were observed in FEV_1, resting PaO_2 on air, BMI, or 6MW distance in either group over the study period.

Table 1 Baseline characteristics of LTOT group and non-LTOT group.

	LTOT group $n = 43$	Non-LTOT group $n = 25$	*P*-value
PaO_2 (kPa)*	6.9 (0.79)	8.8 (0.81)	<0.0001
Male	27 (63%)	18 (72%)	0.44
Age (years)	68 (9.8)	70.6 (6.0)	0.19
Caucasian	39 (91%)	25 (100%)	0.29
Smoking (pack years)	36 (23, 55)	40 (35, 54)	0.35
FEV_1 (%predicted)	31.7 (16.0)	29.6 (12.66)	0.58
$PaCO_2$ (kPa)	6.5 (1.14)	5.7 (0.72)	0.005
BMI (kg/m^2)	24.8 (5.65)	21.6 (4.38)	0.017
6MWD (m)†	251 (112)	331 (125)	0.014
CRQ (disease-specific)			
Dyspnoea (5–25)	15.8 (5.49)	17.4 (4.59)	0.20
Fatigue (4–28)	13.2 (4.67)	16.1 (4.64)	0.016
Emotional function (7–49)	30.8 (8.10)	36.0 (7.69)	0.014
Mastery (4–28)	16.7 (6.03)	20.4 (4.79)	0.009
Total (20–140)	76.7 (20.27)	89.8 (17.42)	0.009
COOP (generic)			
Total (9–45)	25.6	23.2	0.059
HAD			
Anxiety (0–21)	6.7 (4.20)	4.6 (3.45)	0.042
Depression (0–21)	5.4 (3.15)	4.7 (2.90)	0.37

Note higher scores in COOP, HAD indicate worse HRQL higher scores in CRQ indicate better HRQL.
*Selection criterion.
†$n = 36$, 25 respectively.

Table 2 Changes in health-related quality of life at 2 and 6 months for the LTOT and non-LTOT groups.

	LTOT group		Non-LTOT group	
	Change 2 months $n = 42$	Change 6 months $n = 38$	Change 2 months $n = 42$	Change 6 months $n = 38$
CRQ*				
Dyspnoea	2.36 (0.48, 4.23)	2.82 (0.49, 5.15)	0.52 (−1.25, 2.29)	−0.40 (−2.59, 1.79)
Fatigue	2.00 (0.57, 3.43)	1.92 (0.08, 3.77)	0 (−1.58, 1.58)	−0.16 (−1.77, 1.45)
Emotional	2.43 (0.36, 4.50)	2.42 (−0.25, 5.10)	−0.36 (−2.33, 1.61)	−1.40 (−3.39, 0.59)
Mastery	1.55 (0.21, 2.88)	2.39 (0.94, 3.85)	0.12 (−1.04, 1.28)	−0.72 (−2.27, 0.83)
Total	8.10 (3.02, 13.17)	9.26 (2.37, 16.15)	−0.28 (−5.98, 5.42)	−2.56 (−8.31, 3.19)
COOP*				
Total	−1.45 (−3.01, 0.19)	−1.03 (−2.96, 0.91)	−0.32 (−2.31, 1.67)	0.20 (−1.90, 2.35)
HAD*				
Anxiety	−0.81 (−1.71, 0.09)	−1.21 (−2.30, −0.12)	0.36 (−0.82, 1.54)	0.84 (−0.31, 1.99)
Depression	−0.57 (−1.43, 0.29)	−1.42 (−2.47, −0.37)	−0.60 (−1.27, 0.07)	−0.40 (−1.23, 0.43)

*Higher scores in COOP, HAD indicate worse HRQL. Higher scores in CRQ indicate better HRQL.

LTOT responders

The proportion of LTOT responders at 2 months (defined using validated criteria for a minimal clinically significant improvement) for each domain of the CRQ were as follows; dyspnoea 35%, fatigue 51%, emotional function 32%, mastery 40%. In total there were 28 (67%) and 26 (68%) responders at 2 and 6 months, respectively. Generally response at 2 months was predictive of response at 6 months; only 2 (5%) of responders at 6 months had not demonstrated a response at 2 months. Conversely 1 (3%) of responders at 2 months did not show ongoing response at 6 months.

Predictors of LTOT response

Baseline characteristics (gender, resting PaO_2 on air, $PaCO_2$, Borg dyspnoea score, FEV_1, 6MWD, CRQ dyspnoea, emotional function, mastery, fatigue, total, HAD scores) were not predictive of a clinically significant improvement in HRQL at 2 or 6 months. The only predictor identified was hours of oxygen use; every 1 h increase in oxygen use increased the odds of being a responder by 30% (odds ratio 1.3, 95% CI 1.06, 1.57, $P = 0.01$). The mean use of the oxygen concentrators over a 24 h period as was 14.6 (3.7) h (using the hour meter). The proportion of patients using at least 15 h daily was 60% ($n = 25$).

Patient expectations regarding LTOT

The majority of patients either agreed 15 (35%) or strongly agreed 15 (35%) at baseline that LTOT would improve their HRQL with only 8 (19%) disagreeing and 2 (5%) strongly disagreeing. Following the introduction of LTOT only 4 patients who had previously agreed or strongly agreed that oxygen would improve their HRQL indicated that they now disagreed or strongly disagreed. Conversely 6 patients who had (strongly) disagreed now (strongly) agreed that oxygen would improve their HRQL. Patients' expectations regarding LTOT were not predictive of LTOT response.

Discussion

The major finding of this prospective longitudinal interventional study was the significant improvement in HRQL following the introduction of LTOT to patients with severe COPD who fulfilled accepted eligibility criteria. Prior to this study, the results of a very limited body of work, as summarised earlier, have been generally unconvincing with regard to the effect of LTOT on HRQL.

There are very few longitudinal studies which have examined the effect of HRQL on LTOT possibly reflecting the logistic difficulties of such studies and the inability to incorporate a placebo-control on ethical grounds. Nevertheless this is an important question requiring a definitive answer. HRQL is a important endpoint for patients with severe symptomatic COPD; it might be argued that such patients may weight improved HRQL higher than the possibility of living slightly longer.

However the evidence, up to now, that LTOT is beneficial with respect to HRQL has not been compelling. Okubadejo et al.[14] using a study design

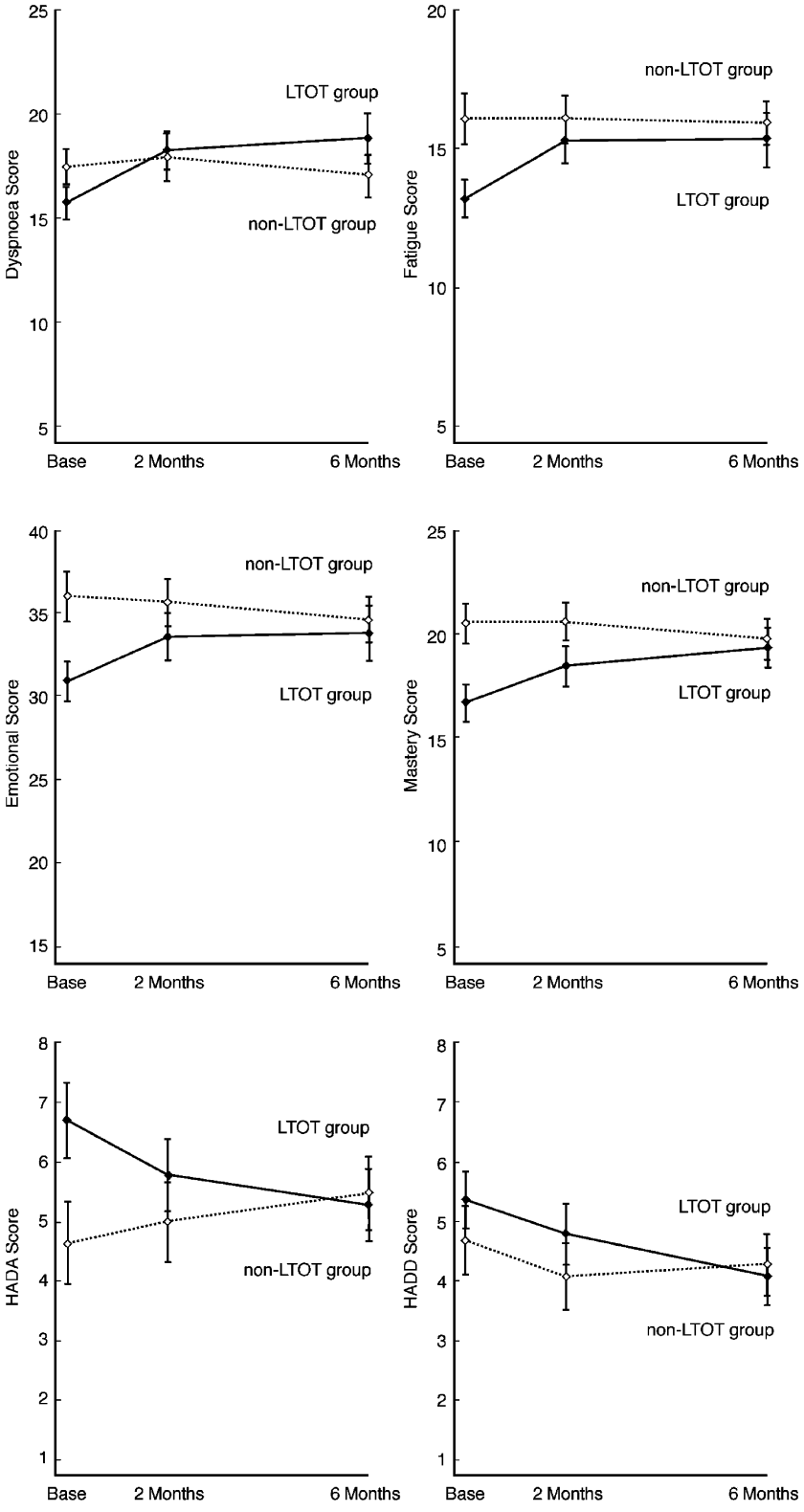

Figure 2 Changes in HRQL by CRQ domain and Hospital Anxiety and Depression scale at 2 and 6 months for the LTOT and non-LTOT groups.

similar to that employed in this paper, were unable to show a change in HRQL (using the disease-specific Saint George's Respiratory Questionnaire) over a 6 month period, although this was a small study ($n = 23$) and hence may have been under-powered. Our study was both larger and employed

the CRQ, an alternative disease-specific tool which may possibly be more responsive.[22] Crockett et al.[15] did report clinically significant improvements in HRQL at 3 months in females, albeit with a less convincing response in males. Although there is increasing recognition of gender differences in response to cigarette smoking, response to other COPD management strategies, COPD mortality and possible perception of HRQL, our study did not support this apparent gender differential.

The absence of a placebo-control is unavoidable. We fully acknowledge the results from the non-LTOT group must be interpreted with caution. However, they were recruited consecutively from the same COPD population referred for LTOT, although did not fulfil criteria for LTOT. HRQL declined in this group despite ongoing standard optimal care over the 6 month study period analogous to the decline observed in the ISOLDE study.[25] This strengthens the contention that improved HRQL in the LTOT group might be directly ascribable to the introduction of LTOT in that all other aspects of care were standardised. Our results were further strengthened by a prospective design attempting to minimise potential confounders and inclusion criteria rigorously insisting on a prolonged period of at least 2 months clinical stability prior to commencing LTOT. Furthermore responders were identified using a priori validated definitions of a clinically important change in HRQL.

The relatively short time of 2 months to obtain clinically meaningful improvement in HRQL is striking, in comparison with the time to show improvement in survival, i.e. 500 days in the Medical Research Council study.[2] It is also important to note that HRQL response at 2 months was predictive of sustained or improved response at 6 months. Furthermore, although improvement was relatively modest, it was comparable to other management strategies accepted as a standard of care, such as inhaled bronchodilator therapy and pulmonary rehabilitation.[26,27] In a disease with limited therapeutic options this is of considerable clinical importance.

The mechanism of benefit to HRQL in response to LTOT remains to be determined. A recent study found HRQL to be related to the severity of hypoxemia in patients with severe COPD.[10] It is certainly plausible that that there is a direct effect on HRQL from the correction of hypoxia for a sufficient period. In support of this, our study found that the only predictor of response to LTOT was hours of use. Poor sleep quality in association with frequent arousals seen with desaturation is well recognised in COPD.[28,29] Furthermore, it has been shown in patients with obstructive sleep apnoea that changes in daytime function correlate more closely with degree of nocturnal hypoxemia than frequency of EEG arousals.[30] Hence, although as yet unproven, correction of nocturnal hypoxia with oxygen therapy in COPD patients might improve sleep quality with associated benefit in other HRQL indices. In our study this may have been indirectly reflected in domains such as fatigue where indeed a greater response was noted.

We noted significant improvement in HRQL despite the potential negative impact of LTOT therapy which includes not only physical constraints but nasal cannulae discomfort. However, previous work has suggested that reduced independence could not be directly attributed to restriction imposed by a concentrator.[31] Nevertheless there is some evidence that mode of oxygen delivery is significantly influential with respect to impact on HRQL with liquid oxygen proving superior to oxygen supplied by concentrators in conjunction with cylinder use during ambulation.[16] The improvement in HRQL is in accordance with our recent randomised controlled study. We demonstrated that ambulatory oxygen results in significant improvements in HRQL in COPD patients with exertional desaturation.[32] Ideally LTOT would always be employed in combination with an ambulatory supply for those patients who are ambulant outside the home. However previous work has shown that up to 45% of LTOT patients are housebound[17,18] and thus would not be suitable candidates for an additional ambulatory supply. Hence the results of our study employing a stationary concentrator alone are reassuring in regard to HRQL and will be relevant to the majority of chronically hypoxic patients. Adherence with LTOT is commonly less than ideal. A study from Scotland reported that 44% of patients used their oxygen for less than 15 h daily.[6] Our results were very similar; 40% using their oxygen for less than 15 h daily and a mean use of 14.6 h. The acceptability and tolerability of a therapy such as oxygen are important considerations which are too often neglected. The ultimate balance of clinical benefit versus adverse effect will only be captured if appropriate measures of HRQL are routinely incorporated into clinical management.

We have fully acknowledged the limitations imposed by the lack of a placebo-control; ideally this study might be performed using a cross-over design. Admittedly, there is a potentially powerful placebo response to oxygen therapy and high patient expectations may be significantly influential. We therefore included a measure of patient expectations. The majority of our LTOT patients did

indeed express positive expectations with respect to LTOT at baseline. Importantly, however, we did not find these predictive of HRQL response to LTOT. Our study, although still relatively small was large enough to show a significant benefit over a short-term period. However the effects of LTOT on HRQL over a longer time period remain to be determined. LTOT has not been demonstrated to prolong survival in COPD patients with moderate hypoxemia[33] and hence is not currently prescribed for this group. However, it is possible that LTOT might improve HRQL in patients with less severe hypoxia not currently fulfilling standard criteria for LTOT.

In conclusion this study has demonstrated that the introduction of LTOT was associated with early and significant improvements in HRQL and sustained or further response at 6 months. There can be no argument that this COPD population has very impaired HRQL and thus any intervention shown to improve this, even to a modest degree, would be advantageous. Sole reliance on survival as an outcome may adversely detract from other potentially important benefits from oxygen therapy. Our results support the use of disease-specific HRQL as a primary outcome measure for future studies of oxygen therapy.

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